REMARKS

This Amendment is in response to the Office Action mailed October 1, 2002. Reconsideration is respectfully requested in view of the above amendments and the following remarks.

I. Rejection of Claims 1-7, 11-15 and 45 for Obviousness (Freud, et al. in view of Wilson, et al. and Manz '480)

The Examiner rejects claims 1-7, 11-15 and 45 under 35 USC 103(a) as being unpatentable over Freud, et al. in view of Wilson, et al. and Manz '480.

Independent claim 1 has been amended to specify that the material being crystallized is a protein. The Examiner is asked to recognize the well known difficulty associated with crystallizing proteins. Accordingly, the Examiner is requested to less liberally rely on non-protein crystallization art such as Manz '480 that have nothing to do with crystallization of proteins to support his rejections for obviousness.

Independent claim 1 has also been amended to specify: "within a microfluidic device, delivering material to an enclosed microvolume via one or more lumens that each have a cross sectional diameter of less than 500 microns to form a plurality of different crystallization samples within the enclosed microvolume." As will be explained below, this claim language includes numerous distinctions over the art relied upon by the Examiner.

A. Use of Microfluidic Devices

Claim 1 specifies "within a microfluidic device, delivering material to an enclosed microvolume via one or more lumens that each have a cross sectional diameter of less than 500 microns." As recognized by U.S. Patent No. 6,409,832 to Wiegl, et al. at Col. 6, line 1 to Col. 8, line 31, fluids behave differently in microfluidic volumes than in other larger volumes. For example, "most fluids show laminar behavior in miniature flow structures with channel cross sections below 0.5mm." Wiegl, et al., Col. 6, lines 19-20.

By contrast to a microfluidic device, Freud, et al. teaches that "the ports within the sidewalls of cell chamber 9 which secure probes 5 and 7 to assembly 1 have a diameter in the range of about 5-10 millimeters." The stated diameter (5-10 millimeters) of these ports is very

large relative to the 500 micron diameter of the lumen used to deliver material to the enclosed microvolume specified in claim 1.

Even more significantly, Freud, et al. teaches using a static system as opposed to a flow system when performing protein crystallizations. Thus, unlike the present invention, Freud, et al. teaches **not** to use a lumen to deliver material to cell 9 where the protein crystallization experiment is performed. Rather, Freud, et al. teaches using the DLS photoprobe in a static monomode for protein crystallization. See Freud, et al., Col 7, lines 11-43. In particular, Freud, et al. teaches at Col. 7, lines 12-14 that "this DLS photoprobe assembly is very versatile and has applications **other than just continuous flow dialysis**. For example, a simple plastic cup-like sample cell can be used for routine **static monomode analysis** of small or valuable samples." The ensuing discussion regarding protein crystallography must be interpreted as being Freud's example of a **static** monomode analysis on a small and valuable crystallization sample. Hence, Freud, et al. fails to teach using a lumen to deliver the protein crystallization experiment to cell 9 in addition to also failing to teach using of a microfluidic device.

Since neither Freud, et al., Wilson, et al. nor Manz '480 teach the use of microfluidic devices, none of these references can be viewed as being equivalent or suggestive to the microfluidic device used in the present invention. The Examiner is requested to employ Wiegl, et al. as the primary reference for his rejection which does teach a microfluidic device used to perform protein crystallization.

B. Forming a Plurality of Different Crystallization Samples in an Enclosed Microvolume

Claim 1 also specifies forming "a plurality of different crystallization samples in an enclosed microvolume." In this regard, Claim 1 further specifies that "the plurality of crystallization samples [in the enclosed microvolume comprise] a material to be crystallized and crystallization conditions which vary among the plurality of crystallization samples." None of the cited references (Wiegl, et al., Freud, et al., Wilson, et al. or Manz '480) teach forming a plurality of different crystallization samples in an enclosed microvolume. Note for example that the discrete cell chamber 9 of Freud, et al. has no provisions for housing multiple different crystallization experiments. Note also in this regard that the crystallization chamber 39 in Wiegl, et al. only comprises a single crystallization experiment. Rather, upon careful review, the Examiner will realize that the references consistently teach that each crystallization sample is

positioned in its own separate and discrete volume. Since none of the references, alone or in combination, teach forming "a plurality of different crystallization samples in an enclosed microvolume," the Examiner's rejection is unsupported and should be withdrawn.

II. Rejection of Claims 8-10, 22-37 and 43 for Obviousness (Freud, et al. in view of Wilson, et al. and Manz '480)

The Examiner rejects claims 8-10, 22-37 and 43 under 35 USC 103(a) as being unpatentable over Freud, et al. in view of Wilson, et al. and Manz '480.

A. Independent Claim 37

Applicants bring the fact that claim 37 is an independent claim to the Examiner's attention. The Examiner's rejection in regard to this claim is traversed for all of the reasons provided in Section I above.

B. Claims 22-36

As noted in Section I above, independent claim 1 specifies forming "a plurality of different crystallization samples in an enclosed microvolume." As also noted in the above section, none of the cited references teach or suggest forming a plurality of different crystallization samples in an enclosed microvolume. Claims 22-36 specify different mechanisms that may be used to form and/or maintain the plurality of different crystallization samples in an enclosed microvolume and thus further distinguish the already distinguished cited references. For this further reason, the Examiner is requested to withdraw this ground of rejection.

III. Rejection of Claims 16-21, 38-42 and 44 for Obviousness (Freud, et al. in view of Wilson, et al. and Manz '480)

The Examiner rejects claims 16-21, 38-42 and 44 under 35 USC 103(a) as being unpatentable over Freud, et al. in view of Wilson, et al. and Manz '480.

The Examiner rejects the above claims basically that the claims merely represent a matter of obvious choice or routine optimization. Applicants traverse the Examiner's summary rejection of these claims.

The pending claims specify detecting crystals while in the microvolume by x-ray spectroscopy. It is noted that among the cited references, only Freud, et al. teaches detecting protein crystals while in the device. However, Freud, et al. uses light and not x-ray energy to detect crystals. Furthermore, Freud, et al. does not provide any teaching specifically directed to detecting protein crystals as opposed to detecting other forms of particles. Hence, Freud, et al. provides no customized teaching regarding enabling the detection of protein crystals.

Wiegl, et al., which as discussed above should be the Examiner's primary reference instead of Freud, et al., does not teach analyzing crystals in the microfluidic device. Rather, Wiegl, et al. incorporates a harvesting chamber 40 so crystals can be retrieved and analyzed outside of the device. Thus, Wiegl, et al. teaches away from performing an x-ray spectroscopic analysis of protein crystals in a microfluidic device.

Applicants are the only party to provide teaching as to how x-ray spectroscopic analysis of protein crystals can be performed in a microfluidic device. The Examiner cannot dismiss Applicants' unique teaching to analyze protein crystals via x-ray spectroscopy while still in a microfluidic device as being obvious without citing prior art that teaches (a) performing x-ray spectroscopy while the crystals are still in the microfluidic device; and (b) how to perform this type of x-ray spectroscopy. For these various reasons, Applicants respectfully request that the Examiner withdraw this further ground of rejection.

CONCLUSION

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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U.S. Application Serial No. 09/877,405

Version With Markings To Show Changes Made

Claims 2-6, 22 and 45 have been cancelled.

Claims 1, 25, 26, 27, 28, 29, 33, 34, 35, 36 and 37 have been amended as follows:

1. (Amended) A method for determining crystallization conditions for a [material] protein, the method comprising:

[taking] within a microfluidic device, delivering material to an enclosed microvolume via one or more lumens that each have a cross sectional diameter of less than 500 microns to form a plurality of different crystallization samples [in an] within the enclosed microvolume, the plurality of different crystallization samples comprising a [material] protein to be crystallized and crystallization conditions which vary among the plurality of different crystallization samples;

allowing crystals of the [material] protein to form in the plurality of crystallization samples within the microfluidic device; and

identifying which of the plurality of crystallization samples within the microfluidic device comprise a precipitate or a crystal of the [material] protein.

25. A method according to claim [25] 24, wherein the one or more dividers are formed of an impermeable material.

26. A method according to claim [25] 24, wherein the impermeable material is an impermeable liquid.

27. A method according to claim [25] 24, wherein the impermeable material is an impermeable solid.

28. A method according to claim [25] 24, wherein the one or more dividers are formed of a permeable material.

29. A method according to claim [25] 24, wherein the one or more dividers are formed of a semipermeable material.

33. A method according to claim [25] 24, wherein at least one of the one or more dividers form an interface selected from the group consisting of liquid/liquid, liquid/ gas interface, liquid/ solid and liquid/ sol-gel interface.

34. A method according to claim [25] 24, wherein the one or more dividers are selected from the group consisting of a membrane, gel, frit, and matrix.

35. A method according to claim [25] 24, wherein the one or more dividers function to modulate diffusion characteristics between adjacent crystallization samples.

36. A method according to claim [25] 24, wherein at least one of the one or more dividers is formed of a semipermeable material which allows diffusion between adjacent crystallization samples.

37. (Amended) A method for determining crystallization conditions for a [material] protein, the method comprising:

[taking] within a microfluidic device, delivering material to a plurality of enclosed microvolumes via one or more lumens that each have a cross sectional diameter of less than 500 microns to form a plurality of different crystallization samples [in a] within the plurality of enclosed microvolumes, each microvolume comprising [one] two or more crystallization samples, the different crystallization samples comprising a [material] protein to be crystallized and crystallization conditions which vary among the plurality of different crystallization samples;

allowing crystals of the [material] protein to form in the plurality of crystallization samples; and

identifying which of the plurality of crystallization samples comprise a precipitate or a crystal of the [material] protein.

U.S. Application Serial No. 09/877,405

Clean Copy of Pending Claims Upon Entry of March 3, 2003 Amendment

1. A method for determining crystallization conditions for a protein, the method comprising:

within a microfluidic device, delivering material to an enclosed microvolume via one or more lumens that each have a cross sectional diameter of less than 500 microns to form a plurality of different crystallization samples within the enclosed microvolume, the plurality of different crystallization samples comprising a protein to be crystallized and crystallization conditions which vary among the plurality of different crystallization samples;

allowing crystals of the protein to form in the plurality of crystallization samples within the microfluidic device; and

identifying which of the plurality of crystallization samples within the microfluidic device comprise a precipitate or a crystal of the protein.

2 7. A method according to claim 1 wherein the enclosed microvolume is a lumen.

3 8. A method according to claim 1 wherein the enclosed microvolume is a lumen with a cross sectional diameter of less than 2.5 mm.

4 9. A method according to claim 1 wherein the enclosed microvolume is a lumen with a cross sectional diameter of less than 1 mm.

5 10. A method according to claim 1 wherein the enclosed microvolume is a lumen with a cross sectional diameter of less than 500 microns.

6 11. A method according to claim 1 wherein the enclosed microvolume is a microchamber.

7 12. A method according to claim 1 wherein the enclosed microvolume is at least partially enclosed within a substrate which comprises other enclosed microvolumes which also comprise crystallization samples.

13. A method according to claim 1 wherein the enclosed microvolume is at least partially enclosed within a card shaped substrate.

14. A method according to claim 1, the method further comprising performing a spectroscopic analysis on a precipitate or crystal formed within the microvolume.

15. A method according to claim 14, wherein the spectroscopic analysis is selected from the group consisting of Raman, UV/VIS, IR, and x-ray spectroscopy.

16. A method according to claim 14, wherein the spectroscopic analysis is x-ray spectroscopy.

17. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the microvolume that the x-ray beam traverses contains at least as many electrons as is contained in a material defining the portion of the microvolume that the x-ray beam traverses.

18. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the microvolume that the x-ray beam traverses contains at least three times as many electrons as is contained in a material defining the portion of the microvolume that the x-ray beam traverses.

19. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the microvolume that the x-ray beam traverses contains at least five times as many electrons as is contained in a material defining the portion of the microvolume that the x-ray beam traverses.

20. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the microvolume that the x-ray beam traverses contains at least ten times as many electrons as is contained in a material defining the portion of the microvolume that the x-ray beam traverses.

21. A method according to claim 1, wherein material defining the microvolume defines a groove that reduces a number of electrons that an x-ray beam used to perform x-ray

spectroscopy of a crystal within the microvolume traverses in the process of performing x-ray spectroscopy on the sample within the microvolume.

17 23. A method according to claim 1, wherein the method further comprises forming the plurality of different crystallization samples within the enclosed microvolume.

16 24. A method according to claim 1, wherein one or more dividers are positioned within the enclosed microvolume to separate adjacent crystallization samples within the enclosed microvolume.

18 25. A method according to claim 24, wherein the one or more dividers are formed of an impermeable material.

18 26. A method according to claim 24, wherein the impermeable material is an impermeable liquid.

18 27. A method according to claim 24, wherein the impermeable material is an impermeable solid.

18 28. A method according to claim 24, wherein the one or more dividers are formed of a permeable material.

18 29. A method according to claim 24, wherein the one or more dividers are formed of a semipermeable material.

23 30. A method according to claim 29, wherein the semipermeable material is a gas.

23 31. A method according to claim 29, wherein the semipermeable material is a liquid.

23 32. A method according to claim 29, wherein the semipermeable material is a gel.

18 33. A method according to claim 24, wherein at least one of the one or more dividers form an interface selected from the group consisting of liquid/liquid, liquid/ gas interface, liquid/ solid and liquid/ sol-gel interface.

28 ~~34~~. A method according to claim ~~24~~ 15, wherein the one or more dividers are selected from the group consisting of a membrane, gel, frit, and matrix.

29 35. A method according to claim ~~24~~ 15, wherein the one or more dividers function to modulate diffusion characteristics between adjacent crystallization samples.

30 36. A method according to claim ~~24~~ 15, wherein at least one of the one or more dividers is formed of a semipermeable material which allows diffusion between adjacent crystallization samples.

31 37. A method for determining crystallization conditions for a protein, the method comprising:

within a microfluidic device, delivering material to a plurality of enclosed microvolumes via one or more lumens that each have a cross sectional diameter of less than 500 microns to form a plurality of different crystallization samples within the plurality of enclosed microvolumes, each microvolume comprising two or more crystallization samples, the different crystallization samples comprising a protein to be crystallized and crystallization conditions which vary among the plurality of different crystallization samples;

allowing crystals of the protein to form in the plurality of crystallization samples; and

identifying which of the plurality of crystallization samples comprise a precipitate or a crystal of the protein.

32 38. A method according to claim 16, wherein the x-ray spectroscopy is x-ray diffraction.

33 39. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the crystal or precipitate that the x-ray beam traverses contains at least as many electrons as is otherwise traversed by the x-ray beam when traversing a device comprising the microvolume.

34 40. A method according to claim 16, wherein x-ray spectroscopy is performed such that a portion of the crystal or precipitate that the x-ray beam traverses contains at least three